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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,731	03/04/2005	Nicole Francisca Van Poppel	I-2002-017 US	5787
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Intervet/Schering-Plough Animal Health Patent Dept. K-6-1, 1990 2000 Galloping Hill Road Kenilworth, NJ 07033-0530			EXAMINER HINES, JANA A	
			ART UNIT 1645	PAPER NUMBER
			NOTIFICATION DATE 11/24/2009	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/526,731	Applicant(s) VAN POPPEL ET AL.	
	Examiner JaNa Hines	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 July 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Amendment Entry

1. The amendment filed July 20, 2009 has been entered. Claim 21 has been amended. Claims 1-20 and 36-38 are cancelled. Claims 21-35 are under consideration in this office action.

Response to Arguments

2. Applicant's arguments filed September 16, 2009 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The rejection of claims 21, 28-32 and 34-35 under 35 U.S.C. 103(a) as being unpatentable over Titus et al., (1995. PNAS, Microbio. Vol. 92:10267-10271) in view of Yan et al., (2001. Mol. & Biochem. Parasitol. Vol.112:61-69) is maintained for reasons already of record.

Titus et al., teach the development of a safe live attenuated *Leishmania* vaccine by gene replacement (page 10267). Titus et al., teach the use of live *Leishmania* would provide a superior vaccine (page 10267). However Titus et al., do not teach

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Leishmania comprising a ribosomal protein gene under the control of an inducible promoter.

Yan et al., teach tetracycline regulated gene expression in *Leishmania* (page 61). Yan et al., teach that conventional gene replacements strategies are unlikely to be useful (page 61). Therefore, Yan et al., teach an inducible system that provides stringent regulation of gene expression in *Leishmania* while offering great advantages (page 61). Yan et al., teach that the tetracycline-responsive repressor/operator system is tighter with the consequence that much lower amounts of tetracycline are needed in order to function effectively (page 61-62). Yan et al., teach that the inducer TetR binds to TetO operator and suppresses transcription from the adjacent promoter (page 62). Yan et al., teach the promoter placement in reverse orientation relative to the rDNA transcription locus (page 66). Yan et al., teach that current options for disease control are limited and more effective, less toxic protective vaccines are needed to manage the disease (page 61).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the attenuated live parasite of Titus et al., which incorporates a ribosomal protein gene under the control of an inducible promoter as taught by Yan et al., in order to provide more effective protective *Leishmania* vaccines. One of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an inducible promoter because Yan et al., teach that an inducible system advantageously provides stringent regulation of gene expression in *Leishmania*, thereby allowing much lower amounts of tetracycline in order

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to function effectively. Furthermore, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since Yan et al., teach that conventional gene replacements strategies are unlikely to be useful in the production of stable live attenuated cell lines. Finally it would have been prima facie obvious to combine the invention of Titus et al., and Yan et al., to advantageously achieve less toxic protective vaccines that manage *Leishmania* infections.

Applicants assert that the result of limiting ribosome synthesis, and therefore the replication of the parasite itself after infecting cells, is not suggested in the prior art, and there would be no suggestion of using procedures that may be found in the prior art to use an inducible promoter to control the expression of the ribosomal protein gene. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case however, the tetracycline repressor/operator system has been used to regulate transcription. In the absence of the inducer, TetR binds and suppresses transcription. Thus, the system of Yan et al., teach a promoter that can be switched on and off, regulating the expression of ribosomal protein genes by inhibiting transcription, whereby ribosome synthesis is

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limited, thereby limiting parasite replication in infected cells. Thus applicants' assertion is not persuasive.

Applicants urge that Yan et al., teach insertion of the expression construct into the tubulin gene region or the vicinity of the ribosomal RNA genes, and it is not inserted near the ribosomal protein genes, as in the present invention. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies i.e., the location of the inducible promoter being near the ribosomal gene proteins are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore applicants' assertion is not persuasive.

Applicants argue that Yan et al., is directed to expression of heterologous genes, however, tubulin is a ribosomal protein gene; Thus applicants' arguments are not persuasive. Therefore, one of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an inducible promoter because Yan et al., teach that an inducible system advantageously provides stringent regulation of gene expression in *Leishmania*, thereby allowing much lower amounts of tetracycline in order to function effectively. Therefore applicants' argument is not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. The rejection of claims 21, 28-32 and 34-35 under 35 U.S.C. 102(b) as being anticipated by Wirtz et al., (Science. 1995. Vol. 528(5214), pages 1179-1183) is maintained for reasons already of record. The rejection is on the grounds that Wirtz et al., teach inducible gene expression for *T. brucei* that allows precise control of the expression of genes.

Applicants' urge that Wirtz et al. does not teach the regulation of expression by controlling expression of the ribosomal gene of the parasite. Wirtz et al., teach the TetR mediates very tight transcriptional control of gene expression. Wirtz et al., teach *Trypanosoma brucei*, wherein said parasite comprises the large subunit gene ribosomal protein gene under the control of an inducible promoter. Wirtz et al., teach that the TetR can also be used to control Pol I, Pol II, Tubulin, and the well characterized procyclic acidic repetitive protein gene transcription from trypanosomatid rRNA promoters. Therefore Wirtz et al., controlling the expression of the gene contrary to applicants' statements.

Moreover, applicants' assertions are not persuasive, since Wirtz et al., teach the expression of a ribosomal protein, since ribosomal proteins are any of the proteins that,

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in conjunction with rRNA, make up the ribosomal subunits involved in the cellular process of translation. Therefore, contrary to applicants' arguments, Wirtz et al., meets the limitations of the claims and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The rejection of claims 21-29 and 33-35 under 35 U.S.C. 103(a) as being unpatentable over Sutherland et al., (1996. Experimental Parasitol. Vol. 83:125-133) and Durocher (US 2002/0106720) further in view of Gozar et al., (Int. J. of Parasitol. 1995. Vol. 25 (8): 929-938).

Applicants argue that Sutherland et al., do not teach about ribosomal protein gene expression. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore it would have been prima facie obvious at the time of applicants' invention to apply the attenuated live parasite of Sutherland et al., which incorporates a ribosomal protein gene under the control of an inducible promoter

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as taught by Durocher and Gozar et al., in order to provide a significant advance in the art. One of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an inducible promoter because Durocher and Gozar et al., teach that an inducible system advantageously provides stringent regulation of gene expression in prokaryotes. Furthermore, no more than routine skill would have been required to incorporate the ribosomal protein gene under the control of an inducible promoter since the art teaches the desire and need to control gene expression in a wide variety of expression systems by incorporating a ribosomal protein gene under the control of an inducible promoter.

Thus applicants' arguments are not persuasive and the rejections are maintained.

New Rejection Necessitated By Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 21-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants assert that the ribosomal protein gene is of the parasite and not a heterologous gene. However, the phrase in claim is a relative which renders the claim indefinite. The phrase is not defined by the claim, the specification does not provide a

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standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. As a matter of fact, the specification is drawn to heterologous genes. Page 19, lines 30-35, states that the recombinant gene comprising part of a heterologous gene is used. The specification at page 20, lines 6-11 even teach a heterologous gene is any gene that encodes a protein other than the tet-repressor protein. There appears to be not description or definition of a protein gene of said parasite and no description on whether "the protein gene of said parasite" is meant to heterologous or not. Therefore the meets and bounds of the claim are indefinite and clarification is required to overcome the rejection.

Conclusion

7. No claims allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645